

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
David MEEKER et al. )  
Application No.: 09/884,526 ) Group Art Unit: 1632  
Filed: June 19, 2001 ) Examiner: Shin-Lin CHEN  
For: COMBINATION ENZYME )  
REPLACEMENT, GENE THERAPY AND ) Confirmation No.: 2532  
SMALL MOLECULE THERAPY FOR )  
LYSOSOMAL STORAGE DISEASES )

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

## **REPLY TO OFFICE ACTION**

In response to the non-final Office Action of March 6, 2006, Applicants respectfully request reconsideration in view of the following amendments and remarks. The period for response has been extended by two months to August 6, 2006 by the accompanying Petition for Extension of Time and a fee to be charged to Deposit Account No. 06-0916.

**Amendments to the claims** begin on page 2.

**Remarks** begin on page 3.

**Attachments:** Information Disclosure Statement Form SB/08

Cristiano et al., Proc. Natl. Acad. Sci. USA 90:11548-11552 (1993)  
Brooks, Mol. Genet. Metabol. 68:268-275 (1999)

**AMENDMENTS TO THE CLAIMS**

This listing of claims will replace all prior versions and listings of claims in the application:

1. (Currently Amended) A method of reducing the accumulation of globotriaosylceramide in a subject diagnosed as having Fabry disease comprising:
  - a) administering to the subject a-viral or non-viral an adeno-associated virus (AAV) vector encoding a  $\alpha$ -galactosidase A, wherein the administration of the vector results in targeting of the  $\alpha$ -galactosidase A to the liver and
  - b) subsequently administering to the subject a therapeutically effective amount of an exogenously produced natural or recombinant  $\alpha$ -galactosidase A,  
such that the accumulation of globotriaosylceramide in the subject is reduced.

2-5. (Canceled)

6. (Previously presented) The method according to claim 1 wherein the  $\alpha$ -galactosidase A is a recombinant  $\alpha$ -galactosidase A.

7-16. (Canceled)

17. (Previously presented) The method of claim 1, wherein the exogenously produced natural or recombinant  $\alpha$ -galactosidase is administered intravenously.

18. (Previously presented) The method of claim 1, wherein the viral or non-viral vector encoding a  $\alpha$ -galactosidase A is administered ex vivo.

19. (Previously presented) The method of claim 1, wherein the viral or non-viral vector encoding a  $\alpha$ -galactosidase A is administered in vivo.

**REMARKS**

**Claim Status**

Claims 1, 6, and 17-19 are pending in this application. Applicants have amended claim 1 to more precisely identify the claimed subject matter. Support for the amendment is present in the specification at least at, e.g., p. 28, line 1 to p. 30, line 5 and p. 20, lines 12-13. No new matter is added.

**Telephonic Interview**

Applicants and their representative thank Examiner Chen for the productive interview held on April 13, 2006. In the interview, the Examiner indicated that had not considered the Ziegler and Barbon references submitted in support of the unexpected results because these references were published after the filing of the present application. The Examiner suggested amending the claims to specifically recite AAV vectors and delivery of  $\alpha$ -galactosidase A to the liver. The amendments, now presented, reflect these suggestions. Both points are addressed in detail below.

**Ziegler and Barbon References**

In the Amendment and Submission filed on February 10, 2006, Applicants provided Ziegler and Barbon references to illustrate that the claimed methods entail unexpected technical advantages, more specifically, a reduced immune response to the administered lysosomal enzyme, which in turn leads to higher efficacy. The fact that those references were published after the Applicants' filing date does not justify not considering them for the purposes of unexpected results. Indeed, confirmation of unexpected results often becomes available only post-filing, because "understanding the full range of the invention is not always achieved at the time of filing." *Knoll Pharmaceutical Co. v. Teva Pharmaceutical*, 367 F.3d 1381 (Fed. Cir. 2004).

M.P.E.P. § 2141, subsection III, expressly authorizes post-filing evidence of unexpected results to be used in support of nonobviousness. "There is no requirement that an invention's properties and advantages were fully known before the patent application was filed, or that the patent application contains all of the work done in studying the invention..." *Knoll Pharmaceutical*, at 1385. Thus, the dates of the Ziegler

and Barbon references are not relevant to the inquiry at hand, and the evidence of unexpected results must be considered accordingly.

Targeting to the Liver

The Examiner suggested in the interview that amending the claims to specifically recite AAV vectors and delivery of  $\alpha$ -galactosidase A to the liver should be sufficient to overcome the outstanding § 103 rejection. Applicants have amended the claims as suggested, and request withdrawal of the rejection accordingly.

The phrase "targeting to the liver" is understood by those skilled in the art to encompass targeting of a gene by means of a liver-specific promoter or other means known to those of skill in the art. Support for the claim amendments is also found in the specification. For example, at p. 30, lines 4-5, the specification contemplates the use of AAV for gene therapy as described, for example, in U.S. Patent Nos. 5,753,500 and 5,962,313. Further, at p. 20, lines 12-13, the specification contemplates tissue-specific targeting, and particularly liver-specific targeting. Additionally, the specification incorporates by reference other publications that describe tissue-specific, including liver-specific, targeting of gene therapy. For example, the specification, at p. 33, lines 19-20 and at p. 40, lines 34-36 incorporates by reference Cristiano et al., *Proc. Natl. Acad. Sci. USA* 90:11548-11552 (1993), which relates to "targeted and efficient gene delivery into the liver for gene therapy of hepatic deficiencies" (p. 11548, reference enclosed). (In accordance with M.P.E.P. § 2163.07(b), "information incorporated [by reference] is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed.")

Additional Reasons

The Examiner has rejected claims 1-27 and 38 under 35 U.S.C. § 103(a) as being unpatentable over Schiffmann et al., *Proc. Natl. Acad. Sci. U.S.A.* 97:365-370 (2000) or Desnick et al., *Proc. Natl. Acad. Sci. U.S.A.* 76:5326-5330 (1979), each in view of Ziegler et al., *Hum. Gene Ther.* 10:1667-1682 (1999) and WO 98/11206 to Selden. Applicants traverse this rejection for at least the following additions reasons.

A *prima facie* case of obviousness is proper only if a reference or combination of references (1) teaches or suggests all the present claim limitations, (2) would have provided a suggestion or motivation for one of ordinary skill in the art to make the claimed invention, and (3) would have provided one of ordinary skill with a reasonable expectation of success in so making. M.P.E.P. § 2143.

Thus, in order to establish *prima facie* obviousness, the Examiner must show that a reference or combination of references teaches or suggests all the present claim limitations. However, the references of record do not teach or suggest "administering a vector encoding  $\alpha$ -galactosidase A, and *subsequently* administering a therapeutically effective amount of an exogenously produced natural or recombinant  $\alpha$ -galactosidase A."

As Applicants previously stated, the order in which gene therapy and enzyme therapy are administered is an element of the claimed methods and should not be ignored. None of the cited references teaches the order of steps as claimed, i.e., first by gene therapy, followed by enzyme replacement therapy. Rather, the Examiner argues that "[a]dministration of the alpha-galactosidase A protein before, after, simultaneously, or alternately with a vector encoding alpha-galactosidase A to the subject would be obvious to one of ordinary skill because determining [an] effective schedule of administration is routine optimization of a result-effective variable and is obvious to one of ordinary skill." March 6, 2006 Office Action, at p. 5. Applicants respectfully disagree with this assessment.

The Examiner has not cited a single reference to show that the schedule of administration in general, and as currently claimed in particular, would have been considered to be a result-effective variable. The M.P.E.P. expressly states that a "particular parameter *must first be recognized* as a result-effective variable, i.e., a variable which achieves a recognized result, *before* the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation." M.P.E.P. § 2144.05 (emphasis added).

In fact, a long-felt and persistent need for a non-immunogenic method of treating lysosomal storage disorders had existed in the field prior to the filing of the present

application. For example, Brooks et al. state that in "patients producing neutralizing antibodies, strategies for either immunosuppression or tolerance induction have been trialed to prevent disease progression" and that other strategies had been proposed "to induce tolerance to specific epitopes, even before therapy is initiated" (Brooks et al., *Mol. Genet. Metabol.* 68:268-275 (1999), at 274 and 273 (reference enclosed)).

Although both gene therapy and enzyme therapy were well known treatments for lysosomal disorders prior to Applicants' invention, the prior strategies did *not* solve the need by combining the therapies in a particular order. This fact alone dispels the Examiner's assertion that the choice of the order of administration was "routine optimization." Thus, the Examiner's suggestion that the order of therapies is a routine choice, in the absence of any supporting evidence, is pure hindsight.

Nevertheless, even if the Examiner had constructed a sound *prima facie* case of obviousness, the evidence of unexpected results submitted with the Amendment and Submission filed on February 10, 2006, is more than sufficient to overcome such a case. M.P.E.P. § 2144.08.

For at least the reasons stated above, Applicants request that the rejection under 35 U.S.C. § 103(b) be withdrawn and the claims allowed.

The Examiner is welcome to call the undersigned Applicants' representative with any questions or comments.

Respectfully submitted,

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